UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/743,347	07/26/2001	Robert G. Korneluk	07891/021003	9890

21559 7590 12/03/2004

CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER	
AKHAVAN, RAMIN	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 12/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

11/29/04 RA

Office Action Summary	Application No.	Applicant(s)	
	09/743,347	KORNELUK ET AL.	
	Examiner	Art Unit	
	Ramin (Ray) Akhavan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45,46,48-51,53-58 and 68-103* is/are pending in the application.

4a) Of the above claim(s) *45,46,48-51,53-58 and 68* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *69-103* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/30/01; 12/11/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group XIII, claims 69-103, in the reply filed on 09/20/2004, is acknowledged. Therefore, all remaining claims are withdrawn from consideration and Applicant is reminded that such claims must be cancelled prior to issuance of any of the elected claims. Claims 69-103 are under consideration in this Action.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed on 07/22/1999 (PCT/IB99/01415). It is noted, however, that applicant has not filed a certified copy of the PCT application as required by 35 U.S.C. 119(b).

Furthermore, it is noted that Applicant is claiming priority to previously filed U.S. nonprovisional applications (Oath/Dec., filed 07/26/2001). However, there is no reference to the priority documents (09/121,979, now US 6,159,709; and 09/332,319 now US 6,171,821) anywhere in the specification. It would be appreciated if Applicant would amend the first line of the specification to contain a reference to priority documents including current status (e.g. issued with corresponding number) and relationship to the instant application. It is noted that the current application is a nonprovisional application that entered the national stage after compliance with 35 U.S.C. 371 from an international application filed under 35 U.S.C. 363 before November 29, 2000 (PCT/IB99/01415, filed 07/22/1999). It is further noted that the instant specification is a duplicate of the specification present in U.S. Patent 6,159,709.

Information Disclosure Statement

The information disclosure statement, filed 04/23/2001, fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein, in part, has not been considered. References, for which there are no copies of record, have been crossed through and have not been considered unless explicitly cited in this action.

Specification

The disclosure is objected to because of the following informalities: The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (p. 30, bottom). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

In addition, on page 53 of the specification the phrase, "What is claimed is:" is present. Occurrence of this phrase is inappropriate and it should be deleted. Appropriate correction is required.

Claim Objections

Claim 70 is objected to because of the following informalities: The claim is missing a period, thus is not a complete sentence. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

1. **Claims 69-103 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.**

All the claims recite the phrase, "[the] antisense molecule ...comprising [a/said] base sequence..." It is unclear how this phrase is to be interpreted in determining the claims' metes and bounds. As written, the claims could be interpreted to either contain an antisense molecule with the requisite region of complementary sequences or that in addition to the complementary region there occur additional sequences. The specification only makes reference to antisense molecules without discerning between base sequences and other sequences. As written the antisense molecule could be interpreted to be of any length or only of the prescribed length as defined by the region of complementary sequences. As written, the claims' metes and bounds are indeterminable.

With respect to claims 71-73, base claim 69 recites the phrase, "[the] antisense molecule comprises a base sequence complementary to at least 10 consecutive nucleotides... ", where dependent claims 71-73 are drawn to a base sequence that is at least complementary to 14-18, 25 and 40 nucleotides, respectively. As such the claims metes and bounds are indefinite because it is unclear how a base sequence that contains at least 10 consecutive nucleotides can concomitantly be at least 14-18, 25 or 40 nucleotides in length.

In other words, the dependent claims are drawn conflicting minimum thresholds for complementary sequences as compared to the base claim. Moreover, it is unclear how the term, "complementary", is to be interpreted. The term is not defined in the specification, but as the term is used in the claims, it could be interpreted to mean either that the complementary strand contains a base-for-corresponding-base match as compared to the sense strand (e.g. A for T/U and G for C), or that the antisense molecule contains a stretch of complementary sequences that contain mismatches. For example, if a base sequence is at least complementary by 14-18 nucleotides (claim 71) and there are no mismatches, then the base sequence would be at least complementary to 14 consecutive nucleotides. Put another way, the term "complement" can be interpreted to mean either that there is strict specificity or complementary to the target sequence or that the antisense molecule need not be exclusively complementary but specifically hybridizable so as to interfere with normal function. (e.g. Galderisi et al. J. Cell. Phys. 1999; 181:251-257; p. 255, col. 2, ¶ 2).

In addition, dependent claims 71-73 would be clearer if the term "consecutive" is inserted before the term "nucleotides" (as is indicated in the specification, p. 30). Otherwise, as written the claims could be interpreted as to mean a sequence that is complementary and that can contain mismatches within the prescribed complementary stretch (i.e. at least 14, 25 or 40), but with the base claim requirement of having at least 10 consecutive complementary nucleotides. In sum, as written, the claims' metes and bounds are indeterminable, because depending on the particular interpretation for "complementary" different art can be applied to the rejected claims.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. **Claims 69-73, 77-88 and 99-103 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.**

The claims are drawn to antisense molecules comprising a base sequence that target portions of any X-linked Inhibitor of Apoptosis Internal Ribosome Entry Site (XIAP IRES) transcript or gene. Specific embodiments are drawn to the particular sequence stretches that are complementary to the target nucleic acid molecule for any XIAP IRES (e.g. 10 consecutive sequences in a defined region of any IRES). As such the claims are drawn to a genus of antisense molecules that either inhibit transcription or translation by targeting any XIAP IRES from any source (e.g. any mammal). The written description requirement for a claimed genus may be satisfied by sufficient description of a representative number of species by actual reduction to practice, reduction to drawings or by disclosure relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure or by a combination of such identifying characteristics sufficient to show applicant was in possession of the claimed genus.

The specification discloses two XIAP IRES having the sequences in accordance to SEQ ID NO: 1 and 2 (murine and human respectively; as shown in Figure 5). However, the claims read on a broad genus of antisense DNA or RNA molecules targeting transcription or translation of XIAP IRES from any source (not just mice or men). The vast genus would encompass an enormous number of different structures, which have not been show to be equivalent in structure to function correlation, by either the instant disclosure or by knowledge in the art. For example, a single nucleotide change in a target sequence could determine whether an antisense molecule binds the target sequence to function as antisense (e.g. inhibit translation). Because the antisense molecule is directly defined by the target molecule sequence, one of skill could not envisage all members of the genus as defined by any XIAP IRES, thus could not identify all the antisense molecules as claimed. Such variability is due to mRNA secondary structures, which in turn determine if the antisense molecule indeed functions as an antisense molecule. Put another way, the target sequence determines target structure, which determines whether a complementary sequence functions as an antisense molecule. (See, Branch, AG, TIBS. 1998; 45-50; p. 49, col. 1; indicating that of nearly two thousand antisense molecules screened for a known target sequence that only a handful bound stably to the mRNA due to accessibility of mRNA substructures that form). Therefore, variants for a particular XIAP IRES sequence can themselves form a separate genus of target molecules that define the antisense molecules. For example, a single base change within a target sequence can affect the free energy of a given secondary structure, which would determine whether stem loop structures form, thus providing regions that are accessible for hybridization. (See, Galderisi et al. J. Cell. Phys. 1999; 181:251-257, at p. 252, col. 1).

Therefore, the claims are drawn to an enormous scope of different structures, which are prone to high variability due to slight changes in their nucleotide sequences. It would be evident that the ability of a given antisense molecule to inhibit translation by binding a XIAP IRES would have to be determined empirically, because inhibition of translation/transcription cannot be predicated by simple complementary base pairing. In other words, one antisense molecule is not necessarily equivalent to another for a given target sequence, in functioning to inhibit translation/transcription. Moreover, it is important to note that antisense molecules that target mRNA are not necessarily interchangeable or equivalents in inhibiting transcription, i.e. targeting DNA (e.g. triplex formation). Indeed, relative to mRNA targeting, there is even less known about structure to function correlation for triplex formation to prevent transcription. However, similar to mRNA targeting triplex formation is affected by single base variants in the duplex target DNA, which affect the stability of the triplex formation. (See, Crooke, ST. *Antisense Research and Application*. 1998 New York, Springer; pp. 569-574). In addition, design and construction triplex forming antisense molecules is constrained by the fact that such molecules are limited to hybridization with purine bases composing polypurine-polypyrimidine tracks within the target DNA. (Jen et al. Stem Cells. 2000; 18:307-19; p. 308, col. 1 bridging ¶ to col. 2). "The targeting efficiency of TFOs [triplex forming oligos] is further constrained by...[the] need for divalent cations...[and most importantly] access to DNA compacted within the chromosome structure." (Id.). Therefore, simply disclosing a sequence that encompasses an XIAP IRES would not necessarily allow one of skill to envisage the antisense molecule structures that can function to inhibit transcription by binding DNA in the nucleus.

Given the enormous breadth of the antisense molecules encompassed by the rejected claims, and given the limited description from the instant specification of such molecules, the skilled artisan would not have been able to envision a sufficient number of specific embodiments to describe the broadly claimed genus of antisense molecules targeted to any XIAP IRES from any source. Moreover, an applicant claiming a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from other species. Therefore, the skilled artisan would reasonably have concluded that applicants were not in possession of the claimed invention.

Therefore the general knowledge and level of skill in the art do not supplement the omitted description for a sufficient representative number of XIAP IRES structures. Since the disclosure fails to describe common attributes or characteristics that identify the members of the genus and because the genus is highly variable, the disclosed sequences of SEQ ID NO: 1 and 2 are not sufficient to describe the claimed genus. (See MPEP § 2163; indicating that a sequence described by functional characteristics, without any known/disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic to fulfill the written description requirement, even when accompanied by a method of obtaining the claimed sequence).

3. **Claims 99-103 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.**

The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The test for enablement is whether one skilled in

the art could make use the claimed invention from the disclosure in the specification coupled with information known in the art without undue experimentation. *United States v Telectronics Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor but instead is a conclusion reached by weighing many factors which are outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). The factors include the following:

Scope/Breadth of the claims. The claims are enormously broad drawn to method of treating any cancer in any cell/tissue in any subject using antisense molecules that target either mRNA or DNA that represents any XIAP IRES to inhibit transcription or translation. Furthermore, the antisense molecules can be RNA or DNA and can be delivered by any means or mechanism into the cell cytoplasm/nucleus.

Nature of the invention. Generally the invention is directed to antisense therapy. The claims are drawn to a method of treating cancer in a subject using antisense molecules that inhibit transcription or translation, reducing XIAP levels in cells, thus increasing the cell's susceptibility to apoptosis. The antisense molecules are delivered into the cell cytoplasm or nucleus to effect binding to target sequences (i.e. XIAP IRESs). The methods and pharmaceutical compositions require *in vivo* applicability and the correlation between antisense compound hybridization to target sequences *in vivo* with the reduction of XIAP protein, thus directly resulting in apoptosis of cancerous cells.

State of the art/Unpredictability of the art. The state of the art for antisense therapy in humans is still developing with some progress. However, there are many more questions about antisense that remain to be answered, with limitations for such technology grounded in

pharmacokinetic and toxicological properties. (See generally, Crooke, ST. Curr. Mol. Med. 2004; 4:465-87; p. 484, col. 2). For proof of mechanism, a number of factors are recommended including, dose response analysis, examination of different classes of oligonucleotides/antisense molecules, determination of potency, demonstration of proposed mechanism of action, evaluation of the therapeutics' specificity and evaluation of non-antisense effects. (Id., p. 466, col. 1).

Generally, the antisense molecules operate by either an RNase H-dependent degradation of the target mRNA or by positional antisense molecules that operate as steric-blockers that physically prevent or inhibit the progression of splicing or translational machinery (as in instant invention). Irrespective of the mechanism, antisense molecules must be delivered into cells, the precise mechanism for which is unclear. Delivery can be via naked oligonucleotides or through vectors, but "all clinical trials with antisense oligonucleotides are carried out with naked oligonucleotides." (Diaz et al. Mol. Cancer Therap. 2002; 1: 347-55; p. 351, col. 2, ¶ 2).

The art of antisense therapy of cancer is unpredictable in many respects. For example, a variety of factors can affect the behavior of antisense molecules *in vivo*, including oligonucleotide purity, structural modifications, target RNA structure and substructure, variability in cellular uptake and differential tissue- or organ-distribution, non-target binding, degradation before delivery or binding and metabolism of antisense molecules *in vivo*. (See supra, Crooke, 1998; pp. 3-7). One of the major problems in targeting mRNA is that within cells the transcripts exist in secondary structures and substructures that maybe further dominated by interactions with cytoplasm proteins. As such, the actual target sequences for a given antisense molecule may actually be inaccessible, thus leading to the requirement for much empirical data.

In this regard, computer programs that generate three-dimensional folding patterns based on free energy calculations often provide results with no meaningful *in vivo* relevance. (Supra, Jen et al. 2000; p. 313, col. 1, ¶ 3). Therefore, simply knowing the sequence for a particular mRNA is not enough.

Non-target affects are particularly salient in evaluating unpredictability, indeed, "the antisense field has been turned on its head by the discovery of non-antisense effects, which occur when a nucleic acid drug acts on some molecule other than its intended target – often through entirely unexpected mechanisms." (See supra, Branch, 1998; p. 45, col. 2). Such non-antisense effects include the antisense molecules binding non-target proteins with unexpected and unpredictable outcomes, such as affecting housekeeping genes and related proteins. (See supra, Crooke, 1998; pp. 3, 13, 277). In addition, there is unpredictability with respect to the particular antisense molecules toxicity *in vivo*, which may be independent or dependent on the particular sequence. For example, either the native or modified antisense molecule can cause immune activation, which can in turn be dependent on the antisense molecule concentration or length. (Id., p. 243). One such immune reactivity is activation of tumor necrosis factor, which can actually lead to tumor death, but not through any antisense binding mechanism. (Id.). Antisense molecules have also been shown to activate SP1 transcription factor, thus affecting cell proliferation and differentiation. (e.g. Biroccio et al. Oncogene. 2003; 22:6579-88; p. 6579, col. 2). Toxicity can also involve hematological effects, such as anticoagulation, thrombocytopenia, anemia and complement activation. (Id., pp. 233-237).

It should be noted that even a single base difference between antisense molecules deems inappropriate any direct correlation between results obtained for an XIAP from one particular

source (e.g. murine) as compared to another (e.g. human) with respect to predictability of toxicity. (e.g. Hu et al. Clin. Cancer Res. 2003; 9:2826-36; p. 2835, top).

As pointed out previously, a major limitation for antisense therapeutics is that delivery can be problematic. (e.g. Jen et al. Stem Cells. 2000; 18:307-19; p. 313, col. 2). For example, antisense molecules can be delivered into non-target genes and actually integrate, thus leading to mutagenesis. (Supra, Crooke, 1998; p. 27). Although an integration event may be rare, it is merely one of a milieu of factors that figure into the unpredictability analysis. Another problem with delivery is that even *in vitro* there is great variation between different cell types with respect to antisense molecule internalization and uptake. (Supra, Galderisi et al. 1999; p. 252, col. 2). Moreover, "extrapolations from in vitro uptake studies to predictions about *in vivo* pharmacokinetic behavior are entirely inappropriate and, in fact, there are now several lines of evidence in animals and man demonstrate[ing] that, even after careful consideration of all *in vitro* uptake data, one cannot predict *in vivo* pharmacokinetics of the compounds based on *in vitro* studies." (Crooke, 1998; p. 3). Pharmacokinetics and toxicity have broad and unpredictable implications in various animal models, such as simian and murine models. (e.g. Crooke, 2004; p. 469, col.1 bridging ¶ to col. 2; p. 471, col. 1 bridging ¶ to col. 2; pp. 481-2; for further discussion of toxicities related to antisense molecule treatment regimes). In addition, the antisense molecules would have to be delivered to nearly every tumor cell in order to be effective..." (Curiel, DT. Breast Cancer Res. 2000; 2:45-49; p. 48, col. 1, ¶ 3). One reason for such comprehensive delivery is that target genes in cancer cells (e.g. XIAP) are often over-expressed, thus require high-level inhibition.

Furthermore, "considering the multitude of molecular entities and signaling pathways that regulate the proliferation and the life/death decision in cancer cells, inhibition of a single target gene is not sufficient to suppress tumor growth." (Supra, Biroccio et al. 2003; p. 6585, col. 2, last ¶).

In sum, antisense therapeutics must overcome several obstacles for *in vivo* application whether in inhibiting translation or transcription, where the obstacles include attaining stable intracellular levels and cell delivery, the requirement for evaluation of extensive empirical data, target mRNA structure, accessibility predictions and the lack of computer model *in vivo* relevance, non-antisense effects, toxicity, and the lack of correlation between *in vitro* results and *in vivo* application.

Amount of guidance provided. There is no substantial relevant guidance provided. There is some prophetic and generic guidance provided on how antisense therapeutics can be used to target gene expression. (e.g. Spec., pp. 31-32). The disclosure is actually directed to characterization of untranslated upstream XIAP sequences from human and comparison with murine, including *in vitro* data on reporter assays/cells. Significantly, there is actually no guidance provided as to *in vivo* application of antisense molecules to treat cancer through apoptosis involvement. Therefore, the specification as filed, does not describe an *in vivo* method of inhibiting XIAP expression in cancer cells so as to promote apoptosis, either through inhibition of XIAP translation or transcription.

Number of working examples. There are no relevant working examples provided for *in vivo* therapy of cancer. All the *in vitro* data provided involves vectors and cells containing the

vectors, which are used to characterize the human XIAP upstream region so as to identify potential IRES sequences.

Amount of Experimentation Required. The level of skill in the art required to practice the claimed invention is high. However, given the unsolved hurdles to successful practicing of the invention, the level of unpredictability in the art, the lack of relevant guidance in the instantly filed specification and lack of relevant working examples, it must be considered that the skilled artisan would be required to conduct trial and error experimentation of an undue nature in order to attempt to practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4. Claims 69-83 and 86-98 are rejected under 35 U.S.C. 102(e) as being anticipated by Korneluk et al. (US 6,107,041; hereinafter the '041 patent).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art. This rejection may be overcome either by showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention by another, or by appropriate showing under 37 CFR 1.131.

The claims are an antisense molecule targeting particular regions of any XIAP IRES or the XIAP IRES corresponding to SEQ ID NO: 2.

Limitations that affect functionality of said antisense molecules are of little moment in determining applicability of art, as the claims are directed to products, thus like products regardless of purpose of use or process of making, etc., read on the claimed products. The term "complementary" is interpreted as broadly as reasonable to mean that there can be mismatches, as between the probe (or antisense molecule) and the target sequence. In addition, stringent hybridization is interpreted as broadly as reasonable to mean specific hybridization, in light of what is known in the art and in light of the definition provided in the specification being non-exclusive. (See Spec. p. 18, l. 15; not limiting the limitation to one specific embodiment). In addition, with respect to claims that define a particular parameter within which consecutive nucleotides that are complementary occur – claims 77-82 – the claims as written are interpreted as being directed to any sequence with the requisite number of consecutive nucleotides, since the claims are not explicitly limited to any particular XIAP IRES (i.e. do not contain any SEQ ID NO designation that would limit the art).

The '041 patent discloses that antisense molecules that can be targeted to various portion of inhibitor of apoptosis (IAP) gene. (e.g. Abstract). In addition, the '041 patent discloses a nucleic acid sequence, SEQ ID NO: 9, with the structural limitations of the instant claims (e.g. SEQ ID NO: 2). With respect to composition claims, the following is applicable:

> "The PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristic of his claimed product. Whether the rejection is based on inherency under 35 USC 102, on prima facie obviousness under 35 USC 103, jointly or alternatively, the burden of proof is the same...". The burden of proof is similar to that required with respect to product-by-process claims. *In re Fitzgerald*, 619 F.2d 67, 7, 205 USPQ 594, 596 (CCPA 1980)(quoting *In re Best*, 562 F.2d 1252, 1255, 195, USPQ 430, 433-34 (CCPA 1977)).

Therefore, the '041 patent anticipates the rejected claims.

5. **Claims 69-83 and 86-98 are rejected under 35 U.S.C. 102(e) as being anticipated by Korneluk et al. (US 6,133,437; hereinafter the '437 patent).**

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art. This rejection may be overcome either by showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention by another, or by appropriate showing under 37 CFR 1.131.

The '437 patent discloses that antisense molecules against IAP fragments. (e.g. Abstract). Furthermore, the '437 patent discloses SEQ ID NO: 9 which corresponds to instant application's SEQ ID NO: 2. As discussed above, the claims are directed to a product so that a like product with inherent or intrinsic properties reads on the invention.

> "The PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristic of his claimed product. Whether the rejection is based on inherency under 35 USC 102, on prima facie obviousness under 35 USC 103, jointly or alternatively, the burden of proof is the same...". The burden of proof is similar to that required with respect to product-by-process claims. *In re Fitzgerald*, 619 F.2d 67, 7, 205 USPQ 594, 596 (CCPA 1980)(quoting *In re Best*, 562 F.2d 1252, 1255, 195, USPQ 430, 433-34 (CCPA 1977)).

Therefore the '437 patent anticipates the rejected claims.

6. **Claims 69-83 and 86-98 are rejected under 35 U.S.C. 102(e) as being anticipated by Au-Young et al. (US 2004/0010136 A1; hereinafter the '136 Application).**

The '136 Application teaches compositions comprising a plurality of probes (i.e. sequences that are complementary or that can hybridize to target sequences).

In addition, the reference discloses SEQ ID NO: 1053, which corresponds to nucleotides 239 to 299 of SEQ ID NO: 2. Therefore, the '136 Application anticipates the rejected claims.

7. **69-75, 77-83, 86-90, 92-94 and 98 are rejected under 35 U.S.C. 102(e) as being anticipated by Korneluk et al. (US 2002/0120121 A1; hereinafter the '121 Application).**

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

The '121 Application, discloses antisense molecules that bind specific sequences of IAP fragments and discloses SEQ ID NO: 9 which corresponds to positions 1-163 of instant application's SEQ ID NO: 2 (or actual SEQ ID NO: 21). Therefore, the '121 application anticipates the claimed product.

8. **Claims 69-70, 75-83, 86-88 and 90-98 are rejected under 35 U.S.C. 102(e) as being anticipated by Cohen et al. (US 6,537,751; hereinafter the '751 Patent).**

The '751 application teaches probes and primers that can bind the various sequences disclosed (e.g. under "Summary of the Invention"), one of which is SEQ ID NO: 2928, which discloses the same structure as instant application's SEQ ID NO: 5 corresponding to positions –46 to –35 of SEQ ID NO: 2. (i.e. tgttctcttttt).

9. **69-74, 76-79, 83, 6-88, 91-94 and 98 are rejected under 35 U.S.C. 102(e) as being anticipated by Korneluk et al. (US 2002/0187946 A1; hereinafter the '946 Application).**

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

The '946 application teaches primers and probes that bind specific sequences disclosed, which include SEQ ID NO 3 which corresponds to positions –53 to –83 of instant SEQ ID NO: 2 (or SEQ ID NO: 25).

10. **Claims 69-70, 76-83, 86-89, 91-93 and 95-98 are rejected under 35 U.S.C. 102(e) as being anticipated by Black et al. (US 6,348,328; hereinafter the '328 Patent).**

The '328 patent discloses that primers and probes can be used to bind the disclosed sequences, which include SEQ ID NO: 6 (gtttcttagcggtcg). This structure meets the requirement for the structure of instant application's SEQ ID NO: 7 (or positions –153 to –139 of SEQ ID NO: 2). Therefore, the '328 patent anticipates the rejected claims.

11. **Claims 69-70-75, 80-83, 86-88, 90 and 95-98 are rejected under 35 U.S.C. 102(e) as being anticipated Korneluk et al. (US 6,6,300,492; hereinafter the '492 Patent).**

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

The '492 patent discloses a sequence, SEQ ID NO: 9 that corresponds to instant SEQ ID NO: 2 from positions –268 to –35 (or SEQ ID NO: 29) and the reference teaches that antisense nucleic acids can bind the target IAP sequences.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

12. **Claims 69-98 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 8 and 9 of U.S. Patent No. 6,159,709 (hereinafter the '709 patent).**

Although the conflicting claims are not identical, they are not patentably distinct from each other. The instant claims are drawn to particular antisense molecules that contain base sequences with complementary sequences to portions of the disclosed sequence structures (i.e. SEQ ID NO: 2, 5, 7, 21, 25, 27 and 29) with at least 10 consecutive nucleotides. Reference claims 8 and 9 are directed to antisense molecules having at least 10 consecutive nucleotides as directed to target sequences of SEQ ID NO: 2. Furthermore, the reference disclosure discloses SEQ ID Nos: 2, 5, 7, 21, 25, 27 and 29, as well as relating the sequences to the characterized XIAP IRES sequence (Figure 5 in both the instant and reference application, as the specifications are identical).

Therefore, instant claims cannot be considered patentably distinct from claims 8 and 9 of the '709 patent. One of ordinary skill in the art examining the '709 patent's claims would have been motivated to examine the full disclosure, including Fig. 5 and the corresponding sequence disclosure to fully understand the identity of the target sequences as related to the claimed antisense molecule.

It would have been obvious to one of ordinary skill in the art to modify the antisense molecules of the '709 patent consonant with the reference patent's disclosure of the full upstream sequence characterized as the XIAP IRES as depicted in Fig. 5. One of skill would have been motivated to do so to design antisense compounds that span the full range of the characterized IRES sequence to ensure hybridization given mRNA's secondary structure and the lack of accessibility for hybridizing molecules. Given the skill at the time of invention and the knowledge in the art with respect to antisense technology, there would have been a reasonable

expectation of success in modifying the antisense molecules of the '709 patent with what was then disclosed in the '709 patent's disclosure.

13. **Claims 69-98 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 24 of U.S. Patent No. 6,171,821 B (hereinafter the '821 patent).**

Although the conflicting claims are not identical, they are not patentably distinct from each other. Claim 24 is drawn to an antisense molecule that targets the XIAP IRES and has at least 10 consecutive complementary nucleotides, with the target corresponding to SEQ ID Nos: 2 or 19-30. Therefore, both the reference claim 24 and the instant claims are directed to antisense molecules that are targeted to SEQ ID NO 2 (human XIAP IRES) and corresponding spans within the characterized IRES sequence (or SEQ ID NOs: 5, 7, 21, 25, 27 and 29) which are disclosed in the reference disclosure.

Therefore one of ordinary skill in examining claim 24 would have been motivated to examine the full disclosure to determine the full scope of the claimed invention and in so doing, the skilled artisan would be further motivated to modify the antisense molecules necessary to practice the invention of reference claim 24 to target the various portions of SEQ ID NO: 2, as claimed in the instant application, because by doing so one would obtain broader coverage of potential mRNA targets in the cell for antisense inhibition. Given the level of skill in the art at the time of invention, one of skill would have a reasonable expectation of success to design such antisense molecules based on the full disclosure of the '821 patent.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ray Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached between 8:30-5:00, Monday-Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD, can be reached on 571-272-0781. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully submitted,

Ray Akhavan/AU 1636

GERRY LEFFERS
PRIMARY EXAMINER